REMARKS

Claims 141 and 144-174 are currently pending. These claims have been amended to reflect the Examiner's modification of the restriction requirement such that all alanine compounds (i.e., integrin antagonist) will be examined in combination with celecoxib.[1] New claims 145-174 are supported by the specification and do not contain new matter.[2]

I. 35 U.S.C. §103(a) Rejection

Reconsideration is requested of the rejection of claims 141 and 144 under 35 U.S.C. §103(a) in view of U.S. Patent No. 6,372,719 ('719 Patent) and International Publication No. WO 98/16227.

Claim 141 is directed toward a method to treat or prevent a neoplasia disorder in a mammal. The method comprises administering to the mammal a therapeutically-effective amount of celecoxib in combination with an alanine-containing, integrin antagonist selected from ten recited compounds.

WO 98/16227 discloses a class of methylsulfonylbenzene or sulfonamidebenzene cyclooxygenase-2 selective inhibitors that are described as being useful for "preventing and treating neoplasia" and in particular, "preventing and treating epithelial cell neoplasia."[3] According to WO 98/16227, their compounds may also be used in co-therapies with any one of approximately 350 compounds described as

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[1]Paper 10 at page 2. Claims 141 and 144 have been amended by adding all of the alanine integrin antagonists present in each claim as filed, but that were deleted from each claim via the Applicants' response to the restriction requirement dated May 16, 2003.

[2]Claims 145-154 are supported by pages 11-12 and 163-216 of the specification. Claims 155-174 are supported by pages 46-49 of the specification.

[3]International Publication No. WO 98/16227, abstract.

"antineoplastic agents or other growth inhibiting agents."[4] But nowhere does WO 98/16227 disclose or suggest a combination comprising celecoxib and an alanine-containing, integrin antagonist selected from the ten recited compounds in claim 141.

The '719 Patent discloses a class of integrin antagonists having any of formulae I-XVIII that are described as being useful in combination therapy with "chemotherapeutic agents."[5] According to the '719 Patent, their integrin antagonists may be used in co-therapies with any one of approximately 44 compounds described as "chemotherapeutic agents."[6] Although the '719 Patent discloses one of the ten integrin antagonists recited in claim 141, nowhere does it disclose or suggest combining this compound with celecoxib for use in the treatment of a neoplasia disorder, as required by the method of claim 141.

In the absence of any disclosure of the combination employed in the method of claim 141, a *prima facie* case for obviousness is lacking.

The Office asserts that it would have been obvious to combine two compositions (i.e., celecoxib as disclosed in WO 98/16227 and an alanine-containing integrin antagonists as disclosed in the '719 Patent), each of which is disclosed in the prior art to be useful for same purpose, in order to form a third composition that is used for the very same purpose (i.e., treatment of neoplasia).[7] But WO 98/16227 and the '719 Patent, taken singly or together, provide no basis for this conclusion.

Among the many compounds and classes of compounds WO 98/16227 and the '719 Patent propose, neither WO 98/16227 nor the '719 Patent offer any guidance that would have enabled a skilled artisan to prepare the combination employed in the

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[4]Id., pages 24-28.

[5]U.S. Patent No. 6,372,719, column 3, lines 38-45.

[6]Id., column 6, lines 47-60.

[7]Paper 10 at page 3.

method of claim 141. WO 98/16227discloses approximately **100** cyclooxygenase-2 selective inhibitors and state that any one of them may be co-administered along with any one of approximately **350** compounds described as "antineoplastic agents."[8] In all of the working examples, a cyclooxygenase-2 inhibitor **other than celecoxib** is tested alone and in combination with cyclophosphamide for use in the treatment of lung cancer.[9] But other than the working examples (which disclose the use of a cyclooxygenase-2 inhibitor other than celecoxib) no significance is placed on any particular combination of a cyclooxygenase-2 inhibitor and antineoplastic agent that would motivate one skilled in the art to select celecoxib from the 100 disclosed cyclooxygenase-2 inhibitors for use in combination therapy. Moreover, of the 350 compounds described as "antineoplastic agents," WO 98/16227 fails to even disclose alanine-containing, integrin antagonist on its rather exhaustive list of co-therapy candidates. The '719 Patent merely disclose a class of alanine-containing, integrin antagonists that may be used in co-therapies with any one of approximately 44 compounds described as "chemotherapeutic agents."[10] Of 44 compounds disclosed as candidates for combination therapy, 5-fluorouracil, cyclophosphamide, cisplatin, taxol, and doxorubicin are described as "preferred" and cyclophosphamide and cisplatin are used in all working examples.[11] Furthermore, of the 44 compounds described as "chemotherapeutic agents," the '719 Patent fails to even disclose cyclooxygenase-2 inhibitors on its list of co-therapy candidates. Accordingly, a skilled artisan empowered with the cited art cannot fairly be deemed to be motivated to select celecoxib disclosed in WO 98/16227 and combine it with an alanine-containing, integrin antagonist

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[8]International Publication No. WO 98/16227, pages 9-16 and 12-14.

[9]Id., pages 19-23.

[10]Id., column 6, lines 47-60.

[11]U.S. Patent No. 6,372,719, column 6, lines 49-50; and column 62.

disclosed in the '719 Patent to form a composition for use in treating a neoplasia disorder, as required by the method of claim 141. As stated in MPEP 2143, where there is no motivation to modify a reference as proposed, the proposed modification is not obvious.

For the foregoing reasons, the Office has failed to establish that claim 141 is *prima facie* obvious in view of WO 98/16227 and the '719 Patent. New claims 145-164 depend from claim 141, and are likewise patentable over these references for the reasons stated with respect to claim 141 and by reason of the additional requirements they introduce.

Moreover, claim 144 is also not obvious in view of the cited art. The composition of claim 144 comprises the same components as the composition employed in the method of claim 141. For all of the reasons detailed with respect to claim 141, therefore, the composition of claim 144 is patentable in view of WO 98/16227 and the '719 Patent. New claims 165-174 depend from claim 144, and are likewise patentable over these references for the reasons stated with respect to claim 144 and by reason of the additional requirements they introduce.

II. 35 U.S.C. 112, First Paragraph Rejection

Reconsideration is requested of the rejection of claim 141 under 35 U.S.C. 112, first paragraph. The Office has asserted that this claim is not sufficiently enabled by the specification.

The standard for enablement is whether one of ordinary skill in the art could make or use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation.[12]

[12]U.S. v. Teletronics, Inc., 8 USPQ2d 1217 (Fed. Cir. 1988).

In this case, the specification coupled with information generally known in the art, fully enables a person of ordinary skill to identify and prepare a composition comprising celecoxib and an alanine-containing, integrin antagonists for use in the method of claim 141 **without undue experimentation**. The specification discloses the chemical structure of celecoxib, how to make it, and how to administer it in combination therapy for the treatment of neoplasia.[13] In addition, the specification discloses the chemical structure of the ten alanine-containing, integrin antagonists recited in claim 141, how to make them, and how to administer them in combination therapy for the treatment of neoplasia.[14] The specification also details over 88 examples[15] of neoplasia disorders that may be treated by the method of claim 141 and also contains nine examples[16] that illustrate the use of combination therapy to treat lung cancer, colorectal cancer, breast cancer, prostate cancer, bladder cancer, pancreas cancer, ovary cancer, and central nervous system cancer. In view of this disclosure, a skilled artisan is sufficiently empowered to make and use the method of claim 141 without undue experimentation.

According to the Office, however, the specification is enabling for the specific neoplasia disorders disclosed,[17] but not for neoplasia disorders not specifically

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[13]For the chemical formula of celcoxib, see page 70 of the specification. Description of how to make celecoxib is detailed in U.S. Patent No. 5,466,823. Examples 1-9 on pages 162-216 detail the use of celecoxib in combination therapy to treat a number of different kinds of neoplasia.

[14]For the chemical structure of alanine-containing, integrin antagonists and a description of how to make it, see page 46-49 of the specification. Examples 1-9 on pages 162-216 detail the use of alanine-containing, integrin antagonists in combination therapy to treat a number of different kinds of neoplasia.

[15]See pages 11-12 of the specification.

[16]Examples 1-9 on pages 162-216 detail the use of celecoxib in combination therapy to treat a number of different kinds of neoplasia.

[17]Paper 10 at page 3.

identified in the specification. The Office asserts that "the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to use the invention *commensurate in scope* with these claims."[18] In arriving at this conclusion, the Office relied on In re Wands.[19] In the Wands case, the claim at issue required using an antibody "wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9M^{-1}."[20] The Federal Circuit discussed several of the relevant factors, and concluded that "undue experimentation would not be required to practice the invention."[21] Contrary to the Office's assertion, however, Wands supports the conclusion that claim 141 is sufficiently enabled.

One factor considered in Wands was the "breadth of the claims." The Federal Circuit noted that of 143 candidate antibodies produced by Wands, his testing of just nine and proving the required activity of just four, not even considering countless others which Wands did not make, was sufficient to support claims of the following breadth: "wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9M^{-1}."[22] This breadth, deemed acceptable, is much broader than a claim limited to those antibodies that Wands either produced or tested. Against this background, the breadth of claim 141, in terms of the use of "neoplasia disorder," is reasonable in light of the 88 examples of

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[18]Paper 10 at page 3.

[19]In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

[20]*Id.*, at 8 USPQ2d p. 1402.

[21]*Id.*, at 8 USPQ2d p. 1406.

[22]In re Wands, at 8 USPQ2d 1405.

specific types of neoplasia disorders identified in the specification and nine examples[23] that illustrate the use of combination therapy to treat lung cancer, colorectal cancer, breast cancer, prostate cancer, bladder cancer, pancreas cancer, ovary cancer, and central nervous system cancer. Patent applicants are not required to show a specific example for every possible embodiment of the claimed invention, so long as the specification and the general knowledge of the art would enable one of ordinary skill in the art to make and use the invention.[24]

As a matter of Patent Office practice, a specification that contains a teaching of the manner and process of making and using the invention, as in the present case, **is presumed to be enabled** unless there is reason to doubt the objective truth of the statements contained in the specification. Furthermore, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement made in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.[25] In this case, the Office action does not state sufficient evidence or reasoning that explains why the Office doubts the truth or accuracy for the disclosure supporting claim 141.

For the foregoing reasons, the Office has failed to establish that claim 141 is not sufficiently enabled. Moreover, new claims 145-154 each recite use of the claim 141 combination to treat a specific neoplasia disorder. As acknowledged by the Office, the

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[23]Examples 1-9 on pages 162-216 detail the use of celecoxib in combination therapy to treat a number of different kinds of neoplasia.

[24]In re Borkowski, 164 U.S.P.Q. 642, 645 (CCPA 1970).

[25]In re Marzocchi, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971)(emphasis added).

specification is enabling for the specific neoplasia disorders disclosed,[26] and as such new claims 145-154 are also enabled by the specification.

[26]Paper 10 at page 3.

III. Conclusion

In light of the foregoing, Applicants request entry of the claim amendments, withdrawal of the claim rejections, and solicit an allowance of the claims. The examiner is invited to contact the undersigned attorney should any issues remain unresolved.

It is believed that no fees are due in connection with this Amendment B. If, however, the Commissioner determines a fee is due, he is hereby authorized to charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,

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